

Anorexia nervosa and cancer risk

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Abstract

Objective: Energy restriction reduces the incidence of malignant tumors in experimental animals, but evidence for a similar effect in humans is lacking. To test the hypothesis in humans, we investigated cancer incidence among patients with anorexia nervosa, who have had an extremely low intake of calories for prolonged periods of their lives.

Methods: Patients with anorexia nervosa (2151 women and 186 men) during 1970–1993 were identified in the population-based Danish Psychiatric Case Register and the National Registry of Patients. The cohort was linked to the Danish Cancer Registry, and cancer incidence among cohort members was compared with that of the general population.

Results: The overall cancer incidence among women with anorexia nervosa was reduced by a factor of 0.80 (95% confidence interval 0.52–1.18) below that of the general population on the basis of 25 observed and 31.4 expected cases. Among men, two cases of cancer were observed, both confined to the brain, whereas 0.2 cases were expected.

Conclusions: The finding of a slight reduction in cancer risk among women with anorexia nervosa may support the theory that a low-energy diet may decrease tumor development in humans. However, longer follow-up and control for confounding factors are needed to obtain more convincing evidence.

Introduction

There is substantial evidence in rodents that energy restriction reduces the incidence of spontaneous, chemically induced, and radiation-induced tumors [1–3]. Various mechanisms have been proposed for this observation, including decreased cell proliferation, reduced oxidative damage to DNA, increased DNA repair, and enhanced apoptosis [1–5]. It is not known, however, if such a cancer-protective effect of energy restriction seen in lower mammals also operates in humans.

We investigated this hypothesis by evaluating the cancer incidence among patients suffering from anorexia nervosa. Such patients are characterized by a very low intake of food; one diagnostic criterion for the disease is a weight loss leading to maintenance of body weight less than 85% of normal weight [6]. Patients with anorexia nervosa were identified in population-based and nationwide Danish registers: the Psychiatric Case Register and the National Registry of Patients. All identified patients were followed for cancer occurrence in the Danish Cancer Registry for up to 27 years.

Material and methods

The Psychiatric Case Register contains information on all admissions to psychiatric hospitals and departments in Denmark since 1970 [7]. Each admission gives rise to

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registration of a personal identification number (which includes sex and date of birth), dates of admission and discharge, one main discharge diagnosis, and up to three auxiliary diagnoses. The National Registry of Patients includes similar registrations of admissions to nonpsychiatric hospitals since 1977, but with up to 19 auxiliary diagnoses per discharge. The diagnoses were coded according to the Danish version of the ICD-8 [8] in both registers. Use of the unique 10-digit personal identification number, which is assigned to all residents of Denmark shortly after birth by the Central Population Register, permits accurate linkage of information between registers.

All persons with a diagnosis of anorexia nervosa (ICD-8 = 306.50; $n = 2404$) at the ages of 7–50 years were identified in the Psychiatric Case Register and in the National Registry of Patients from the start of each register until 1993. Patients who also had a diagnosis of oligophrenia (ICD-8 = 310–315; $n = 34$) or dementia (ICD-8 = 290; $n = 15$) were excluded from the study. The cohort was linked to the Central Population Register to obtain dates of death and emigration, and 18 (1%) persons were excluded: one who lived in Greenland, five who had emigrated, and 12 who had died during the hospital admission for anorexia. The final cohort comprised 2337 persons with a diagnosis of anorexia nervosa.

The Danish Cancer Registry, which has almost complete national coverage of malignant neoplasms and benign tumors of the nervous system, papillomas of the urinary system, and cervical neoplasia [9], was used to track all such cases diagnosed among the cohort members. The period of follow-up was from the date of the first discharge with anorexia nervosa until date of death or emigration or 31 December 1996. The expected numbers of cancers were calculated by multiplying the appropriate sex-, age-, and calendar-specific rates by the accumulated person-years. The observed number of cancers divided by the expected number yields the standardized incidence ratio (SIR). Corresponding 95% confidence intervals (CIs) were calculated by Byar's approximation or exact Poisson limits (if the observed number of cancers was less than 10) under the assumption that the observed number of cancers in a specific category follows a Poisson distribution [10].

Results

The large majority (92%) of the patients with anorexia nervosa in the study cohort were women (Table 1), and most of the patients were aged 10–24 years at the time of their first hospitalization with anorexia. Relatively few

Table 1. Characteristics of persons hospitalized with anorexia nervosa, 1970–1993, Denmark

Characteristic	Women (%)	Men (%)
Total number	2151 (100)	186 (100)
Age at anorexia discharge (years)		
7–9	18 (1)	2 (1)
10–14	391 (18)	73 (39)
15–19	724 (34)	51 (27)
20–24	438 (20)	24 (13)
25–29	217 (10)	15 (8)
30–34	138 (6)	7 (4)
35+	225 (10)	14 (8)
Year of anorexia discharge		
1970–1974	149 (7)	17 (9)
1975–1979	421 (20)	40 (23)
1980–1984	539 (25)	50 (27)
1985–1989	568 (26)	39 (21)
1990–1993	474 (22)	40 (22)
Type of hospital department		
Somatic	1311 (61)	124 (67)
Psychiatric	840 (39)	62 (33)

patients entered the cohort at the beginning of the study period, because the Psychiatric Case Register was the only source of patients from 1970 until 1977. Most (61%) of the patients were first hospitalized for anorexia nervosa in a department for somatic diseases.

In total, 25,165 person-years were accumulated in the follow-up of women with anorexia nervosa, corresponding to a mean follow-up time of 11.7 years (range 0–26 years). During this period, 25 cases of malignant neoplasm were observed, while 31.4 were expected, yielding a SIR of 0.8 (95% CI 0.52–1.18) (Table 2). There was no trend in the overall SIR for cancer by time since first hospitalization with anorexia (data not shown). When specific cancer sites were considered, no significant deviation from the expected number was seen (Table 2). The risk for breast cancer was slightly reduced, on the basis of seven observed and 8.7 expected cases, whereas the risk for cervical cancer was reduced by 0.6 times on the basis of two cases. The brain tumor that occurred was a transitional meningioma diagnosed nine years after the first discharge for anorexia nervosa. There were 43 cases of cervical intraepithelial neoplasia (dysplasia and carcinoma *in-situ*) among anorectic women, with 58.6 expected, yielding a SIR of 0.7 (95% CI 0.5–1.0).

The men with anorexia nervosa were followed for an average of 12.5 years (range 0–27 years), accruing 2324 person-years. Two cases of cancer were observed, with 1.5 expected (SIR 1.3; 95% CI 0.2–4.7). Both were brain tumors (0.2 expected; SIR 12.5; 95% CI 1.5–45); one

Table 2. Standardized incidence ratios (SIRs) of cancer among 2151 women hospitalized with anorexia nervosa, 1970–1993, Denmark

Tumor site (modified ICD-7) ^a	Observed	Expected	SIR	95% CI
All malignant neoplasms (140–205)	25	31.4	0.80	0.52–1.2
Buccal cavity and pharynx (140–148)	1 ^b	0.3	3.2	0.1–17.4
Digestive organs (150–159)	3	2.2	1.3	0.3–3.9
Esophagus (150)	1	0.1	20.0	0.5–111
Stomach (151)	1	0.3	3.8	0.1–21.4
Pancreas (157)	1	0.2	4.4	0.1–24.2
Lung (162.0–1)	3	1.4	2.2	0.5–6.4
Breast (170)	7	8.7	0.8	0.3–1.7
Female genital organs (171–176)	2	6.1	0.3	0.0–1.2
Cervix (171)	2	3.7	0.6	0.1–2.0
Urinary system (180–181)	1	0.6	1.6	0.0–8.7
Skin (190–191)	4	6.8	0.6	0.2–1.5
Brain and nervous system (193)	1	1.7	0.6	0.0–3.2
Thyroid gland (194)	1	0.6	1.8	0.0–10.0
Non-Hodgkin's lymphoma (200, 202, 205)	2	0.7	3.0	0.4–10.8
Other specified sites (160, 161, 162.2, 163, 164, 192, 195–197, 201, 203, 204)	0	1.8	–	0.0–2.0
Metastases and unspecified sites (198–199)	0	0.5	–	0.0–7.8
Other neoplasms				
Cervical intraepithelial neoplasia (dysplasia and carcinoma <i>in situ</i>) (571.1, 571.2)	43	58.6	0.7	0.5–1.0

^a The modified version of ICD-7 is shown in reference 9.

^b Cancer of the tongue.

astrocytoma of the frontal lobe in a 32-year-old man nearly 17 years after his first hospitalization for anorexia nervosa, and one craniopharyngioma of the pituitary gland in a 23-year-old man four years after his hospitalization for anorexia nervosa.

Discussion

Our study shows that the incidence of cancer is slightly, non-significantly reduced among women hospitalized for anorexia nervosa, but low statistical power precluded any inference from the results for men.

The collections of data in the nationwide, population-based registers of inpatients at psychiatric and nonpsychiatric hospital departments offered a unique chance to establish a large cohort of patients with nonself-reported anorexia nervosa, although we still had limited power to detect a decrease in the risk for cancer since most of the patients were under 50 years of age during the study period. Use of the unique personal identification number allowed unambiguous linkage between the discharge registers, the Central Population Register and the Cancer Registry, and thus complete follow-up information on deaths, emigrations, and cancer cases among cohort members. Hospitalized patients with anorexia nervosa were chosen to test the energy-restriction

hypothesis because they constitute a well-defined group of persons with a very low intake of calories. We excluded patients with additional diagnoses such as oligophrenia and dementia, because they are not likely to have anorexia nervosa. We did not exclude patients with prevalent cancers (although the cases were not included in the observed number), because the cancer incidence rates used to calculate the expected number of cancers include multiple cancers in one individual. Only six patients out of the total actually had a cancer diagnosed prior to entry, and none of these patients had a second primary cancer. There was no decreasing trend in cancer risk by time since first hospitalization for anorexia nervosa, which reduces the likelihood that patients with undiagnosed cancer but with anorexia nervosa-like symptoms were selected into the cohort. One exception may be the craniopharyngioma observed in a male cohort member: since tumors of the structures of the midline of the brain are known to mimic anorexia nervosa [11], the tumor may well have been the primary disease in this case.

To our knowledge, the present study is the first to investigate the cancer risk among patients with anorexia nervosa. Several studies have been conducted on mortality among such patients [12, 13], but none provided risk estimates for mortality from cancer. In a recent prospective study from the US, men with a body mass index below 18.5 kg/m² had lower cancer

mortality than men of normal weight, while there was no difference in cancer mortality between the leanest women and normal-weight women [14]. In general, the results of epidemiological studies on energy intake and cancer risk are equivocal [15, 16], perhaps due to the difficulties in the assessment of energy intake in epidemiological studies, or to inadequate control for physical activity, which is strongly related to energy intake [17]. Studies of energy intake do not necessarily provide information on the effect of energy restriction if the lowest level of energy intake is higher than the effective level of energy restriction. Studies in experimental animals show that the tumor incidence is reduced only when the energy restriction is greater than 10% [1]. A study of eight obese persons showed a reduction in rectal-cell proliferation when caloric intake was decreased [18], but energy restriction in obesity may not be comparable to restriction in persons of normal weight.

The timing of energy restriction may also be relevant. It has been proposed that energy restriction during puberty reduces the risk for breast cancer later in life, and this hypothesis is supported by an ecological study in which the incidence of breast cancer was found to be lower in women who were experiencing puberty during the Second World War in Norway, when energy intake was lower than that of women experiencing puberty before or after the War [19]. In contrast, a cohort study of women in the Netherlands who suffered severe undernutrition at adolescence during the Second World War provided no clear evidence for the hypothesis [20]. Energy restriction during other periods of growth, such as childhood, may also be relevant, as indicated by an English cohort study in which energy intake during childhood was positively associated with mortality from cancer later in life [21]. A considerable proportion of patients with anorexia are adolescents, but they represented too small a group in our cohort for a separate analysis.

Under experimental circumstances in animal studies, the effect of energy restriction can be studied in animals with sufficient amounts of vitamins and minerals in the diet. In contrast, patients with anorexia tend to be more generally undernourished, and their food intake may simply be too low to assure the fundamental needs or micronutrients that may directly or indirectly (through concomitant diseases) affect the cancer pattern. For instance, nutritional deficiency may be positively associated with esophageal cancer [22]. Many organ systems may be affected by the undernutrition seen in anorectic patients, including the endocrine and hematological systems. Peripheral estradiol concentration is decreased among patients with anorexia nervosa [23], which

might lower the incidence of hormone-dependent cancers such as breast cancer [24]. Anorexia is also associated with immunodeficiency [25], which in other medical conditions has been linked to increased incidences of certain cancers, in particular non-Hodgkin's lymphoma [26].

Patients with anorexia nervosa may differ from the general population in respect to lifestyle. For instance, they tend to have a high level of physical activity [27, 28], which may reduce the incidence of cancers such as colorectal [29] and breast cancer [30]. Conversely, women with anorexia tend to have children later in life and to have fewer children than the average woman [31], and these are risk factors for breast cancer [24]. Sexual functioning is often poor in anorectic women [32], and low sexual activity may be an underlying explanation for the reduced risk of cervical neoplasia [33]. Avoidance of sun exposure in this population of patients may contribute to a decrease in their risk of skin cancer [34]. Mortality was found previously to be increased among the patients with anorexia included in our cohort, primarily due to suicide and anorexia nervosa, but in 10 of 108 deaths from natural causes (excluding anorexia nervosa) the primary cause was alcoholic liver cirrhosis [35]. In accordance with this, alcohol abuse has been positively associated with anorexia nervosa in another setting [36]. Since excess alcohol intake is causally linked to esophageal cancer [22], it may have caused the case of esophageal cancer seen here among anorectic women.

In conclusion, patients with anorexia nervosa differ from the background population in respect to medical constitution and lifestyle factors that may influence their cancer incidence in opposite directions, as described above. The net consequence is difficult to determine. The weakly reduced risk for cancer among women with anorexia found in our study must be evaluated cautiously, although it may support the hypothesis that energy restriction reduces tumor incidence in humans. We intend to continue to follow the cohort of patients with anorexia nervosa for cancer occurrence over the coming years as more cohort members reach ages of higher cancer incidence rates.

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